REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims under examination be allowed.

Amendments in the Specification

The last paragraph on page 2, spanning to page 3, has been amended to recite "C-NT2RP3001495" instead of "C-T2RP3001495" to correct a typographical error. Support for this correction can be found throughout the specification, for example, at page 40, lines 17-25.

Claim Amendments

Claim 1 has been divided to 4 independent claims. Therefore, (b), (c) and (d) of claim 1 have been deleted and included in claims 19, 24 and 30, respectively. Claim 1 is also amended to recite "polypeptide" instead of "protein" to be consistent with the other claims, such as claim 11.

Claim 2 has been amended to recite a function associated with the maintenance of differentiation of smooth muscle cells that is equivalent to that of the protein comprising the amino acid sequence of SEQ ID NO:2. Support for this amendment can be found, for example, at page 5, line 30 to page 6, line 1.

Claims 11 and 12 have been amended to further clarify the polypeptide that is produced and recovered from each of the claimed methods.

New claims 18-62 have been added. Support for these new claims can be found, for example, as follows:

Claim Number	Exemplary Support
18	Page 5, lines 4-7
19	Original claim 1(b)
20-23	Original claims 3, 5, 7 and 11
24-25	Original claim 1(c) and page 6, lines 25-27
26-29	Original claims 3, 5, 7 and 11
30	Original claim 1(d) and page 8, lines 10-11
31-34	Original claims 3, 5, 7 and 11
35-36	Page 10, lines 13-16
37-40	Original claims 3, 5, 7 and 11
41	Original claim 2 and page 5, lines 19-21
42-45	Original claims 3, 5, 7 and 11
46-47	Original claim 1(c); page 6, lines 25-27; and page 5, lines 19-21
48-51	Original claims 3, 5, 7 and 11
52	Original claim 1(d); page 8, lines 10-11; and page 5, lines 19-21
53-56	Original claims 3, 5, 7 and 11
57-58	Page 10, lines 13-16 and page 5, lines 19-21
59-62	Original claims 3, 5, 7 and 11

No new matter has been added by these amendments. The Examiner is hereby requested to enter these amendments.

Applicants submit that all claim amendments presented herein are made solely in the interest of expediting allowance of the claims and should not be interpreted as acquiescence to any rejections or ground of unpatentability. Applicants reserve the right to file at least one

continuing application to pursue any subject matter that is canceled or removed from prosecution due to the amendments.

Election/Restrictions (Paragraphs 1-4 of the Office Action)

The Office Action requires restriction to one of the following inventions under 35 U.S.C. §121:

I. Claims 1-8 and 11-12, drawn to DNA, vectors, host cells and method of making protein, classified in class 435, subclass 69.1.

II. Claims 9-10, drawn to a protein, classified in class 530, subclass 350.

III. Claims 13-14, drawn to an antibody, classified in class 530, subclass 387.1.

IV. Claim 15, drawn to a nucleic acid molecule that hybridizes to SEQ ID NO: 1, classified in class 536, subclass 23.1.

V. Claims 16-17, drawn to a method of screening a compound that binds to the polypeptide, classified in class 514, subclass 2.

Applicants affirm the election of Group I, claims 1-9 and 11-12. However, claim 1 has been divided to 4 independent claims (claims 1, 19, 24 and 30). In addition, newly added claims 18-62 are all drawn to DNA, vectors, host cells and methods of making proteins. Therefore, Applicants submit that Group I now contains claims 1-8, 11-12 and 18-62.

The election was made with traverse for the reasons set forth below.

There are two criteria for a proper requirement for restriction between patentably distinct inventions:

(a) The inventions must be independent or distinct as claimed; and

(b) There must be a serious burden on the Examiner if restriction is not required.

MPEP §803. If the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to independent or distinct inventions. *Id.*

In this case, Groups I and IV can be searched and examined together without serious burden on the Examiner. Group I contains claims directed to isolated nucleic acids, vectors and transformants comprising the nucleic acids, as well as methods of producing polypeptides using the transformants. In particular, claim 1(d) (now rewritten as independent claim 30) is directed to an isolated nucleic acid that hybridizes after washing with 0.1xSSC and 0.1% SDS at 65°C with the nucleic acid consisting of the nucleotide sequence of SEQ ID NO:1, and that encodes a polypeptide having a function associated with the maintenance of differentiation of smooth muscle cells that is equivalent to that of the protein consisting of the amino acid sequence of SEQ ID NO:2. Group IV contains a single claim, claim 15, which is directed to a polynucleotide that hybridizes with the nucleic acid comprising the nucleotide sequence of SEQ ID NO:1 or the complementary strand thereof and that comprises at least 15 nucleotides. Since claims 15 and 30 are both directed to nucleic acids hybridizing to SEQ ID NO:1, the two groups of claims can be searched and examined together without serious burden on the Examiner.

Accordingly, the criterion under MPEP §803(b) is not satisfied. Applicants respectfully request that Groups I and IV be rejoined to a single group containing claims 1-8, 11-12, 15 and 18-62, and that this group be examined.

Rejections Under 35 U.S.C. §101 (Paragraph 5 of the Office Action)

The rejection of claims 1-8 and 11-12 under 35 U.S.C. §101, as allegedly lacking patentable utility, is respectfully traversed for the reasons set forth below.

A patentable utility is specific, substantial, and credible. The utility requirement can be satisfied if the claimed invention has a well-established utility, or if the application asserts a specific and substantial utility that is credible. Utility Examination Guidelines, Federal Register 66(4):1092, 1098 (2001) (hereinafter "the Utility Guidelines").

Claims 1 is directed to an isolated nucleic acid encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2. Claim 2 is directed to an isolated nucleic acid encoding the amino acid sequence of SEQ ID NO:2 or a fragment thereof having a function associated with

the maintenance of differentiation of smooth muscle cells that is equivalent to that of the protein consisting of the amino acid sequence of SEQ ID NO:2. The specification discloses that the protein of SEQ ID NO:2 maintains the differentiated state of smooth muscle cells (page 5, lines 4-9). Abnormalities in the maintenance of differentiation of smooth muscle cells have been known to cause a variety of diseases. For example, phenotypic modulation of vascular tunica media smooth muscle cell to a dedifferentiated type is recognized in the early phases of the onset of arteriosclerosis and is known as the major cause of thickening of vascular endothelium (page 50, last paragraph). Other diseases caused by an abnormality in the maintenance of differentiation of smooth muscle cells include myocardial infarction, aortic aneurysm, cerebral apoplexy, cerebral vascular disorders, vascular dementia, as well as glomerulonephritis, pulmonary fibrosis, cerebral arteriosclerosis, hepatitis, and many others (see, for example, page 51, first paragraph). The specification thus discloses that the protein of SEQ ID NO:2 can be used as a target molecule in drug development (*Id.*) Furthermore, the protein itself, or compounds controlling the function thereof, can be used as pharmaceuticals for these diseases (*Id.* and page 3, lines 19-25).

This asserted utility is specific and substantial, as it involves specifically named diseases that are "real world" medical problems. The asserted utility is also credible, as discussed below.

Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (*e.g.*, test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant's assertions. The Utility Guidelines, Federal Register 66(4), at 1098.

In this case, the specification discloses that SEQ ID NO:1, which encodes SEQ ID NO:2, is preferentially expressed in differentiated smooth muscle cells when compared to their de-differentiated counterparts (Example 6, pages 41-42). The specification further discloses that SEQ ID NO:2 contains two WW domains and is expected to undergo protein-protein interactions and regulate intracellular signal transduction or gene expression, to exert its function in the maintenance of differentiation of smooth muscle cells (page 5, lines 15-19). Indeed, the mouse

ortholog of the protein has been shown to bind p53 and inhibit cell proliferation by apoptosis (see, *e.g.*, Chang *et al.*[1], copy enclosed herewith as Exhibit A). It has been well known in the art that p53 inhibits the growth of vascular smooth muscle cells and plays a pivotal role in regulating the growth of these cells (see, *e.g.*, Aoki *et al.*[2], copy enclosed herewith as Exhibit B). Taken together, the evidence indicates that the protein of SEQ ID NO:2 binds to p53 and inhibits smooth muscle cell proliferation by inducing apoptosis, thereby maintaining differentiation of smooth muscle cells and preventing thickening of vascular walls. The evidence thus further confirms the function of the protein of SEQ ID NO:2 in smooth muscle differentiation and therapeutic application in diseases such as arteriosclerosis, as asserted in the present application. Therefore, one of ordinary skill in the art would consider the utility of the claimed invention in smooth muscle cell differentiation and therapeutic application in diseases such as arteriosclerosis, as asserted in this application, a credible one.

In addition to asserting a specific, substantial and credible utility, the present application also provides several well-established utilities for the claimed invention. An invention has a well-established utility (1) if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (*e.g.*, properties or applications of a product or process), and (2) the utility is specific, substantial, and credible.

The specification discloses that TNF-α reduced the expression level of the nucleic acid of SEQ ID NO:1 in synovial tissue (Example 9). TNF-α is known to participate in the onset of rheumatoid arthritis (see, *e.g.*, Example 9), and artisans have suggested inhibiting TNF-α as a therapeutic approach for rheumatoid arthritis (see, *e.g.*, first paragraph in the right column on

---

[1] Chang *et al.* Hyaluronidase induction of a WW domain-containing oxidoreductase that enhances tumor necrosis factor cytotoxicity. J Biol Chem. 276(5):3361-70 (2001). Chang et al. disclose the murine WOX cDNA and state that the human WOX cDNA is known as WWOX or FOR (see, e.g., page 3962, right column, second last paragraph of Chang at al.) As disclosed in the present application (page 41, lines 15-21), "C-NT2RP3001495" is the same as WWOX.

[2] Aoki *et al.* Inhibition of the p53 tumor suppressor gene results in growth of human aortic vascular smooth muscle cells. Potential role of p53 in regulation of vascular smooth muscle cell growth. Hypertension 34(2):192-200 (1999).

page 3408 of Maskos *et al.*[3], copy enclosed herewith as Exhibit C). Therefore, a person of ordinary skill in the art would have immediately appreciated that the claimed invention can be used as a probe to detect the level of expression of SEQ ID NO:1 mRNA in synovial tissue of a patient to diagnose TNF-α associated rheumatoid arthritis to facilitate the determination of a proper treatment regimen, or as a measure of the effect of TNF-α on the tissue. These utilities are clearly specific, substantial, and credible.

Furthermore, as discussed above, the specification discloses that SEQ ID NO:1, which encodes SEQ ID NO:2, is preferentially expressed in differentiated smooth muscle cells when compared to their de-differentiated counterparts. A person of ordinary skill in the art would have immediately appreciated that SEQ ID NO:1 or SEQ ID NO:2 can be used a marker to distinguish differentiated smooth muscle cells from the undifferentiated or de-differentiated ones. As such, a person of ordinary skill in the art would have further recognized that the marker can be used to monitor the treatment for an associated disease, such as arteriosclerosis, or as the readout in an *in vitro* drug screening assay. The Revised Interim Utility Guidelines Training Materials ("the Utility Training Materials; http://www.uspto.gov/web/menu/utility.pdf) specifically provide that the use as a cellular marker is a well-established utility (see, e.g., Example 12 of the Utility Training Materials, particularly pages 69-70).

Accordingly, the claimed invention satisfies the utility requirement under the Utility Guidelines. Therefore, Applicants respectfully request that this rejection be withdrawn.

Rejection Under 35 U.S.C. §112, First Paragraph, Written Description (Paragraph 6 of the Office Action)

The rejection of claims 1-8 and 11-12 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application

[3] Maskos *et al.* Crystal structure of the catalytic domain of human tumor necrosis factor-alpha-converting enzyme. Proc Natl Acad Sci U S A. 95(7):3408-12 (1998).

was filed, had possession of the claimed invention, is respectfully traversed for the reasons set forth below.

Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, Paragraph 1, "Written Description" Requirement, Federal Register 66(4):1099, 1104 (2001).

Claim 1 (now claims 1, 19, 24 and 30)

As amended, claim 1 has been divided to the following 4 independent claims:

1. An isolated nucleic acid encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2.
19. An isolated nucleic acid comprising the coding sequence of SEQ ID NO:1.
24. An isolated nucleic acid encoding a polypeptide that comprises the amino acid sequence of SEQ ID NO:2, in which up to 10 amino acids are replaced, deleted, and/or inserted, wherein said polypeptide has a function associated with the maintenance of differentiation of smooth muscle cells equivalent to that of the protein consisting of the amino acid sequence of SEQ ID NO:2.
30. An isolated nucleic acid that hybridizes after washing with 0.1xSSC and 0.1% SDS at 65°C with the nucleic acid consisting of the nucleotide sequence of SEQ ID NO:1, and that encodes a polypeptide having a function associated with the maintenance of differentiation of smooth muscle cells that is equivalent to that of the protein consisting of the amino acid sequence of SEQ ID NO:2.

The present specification describes sufficient distinguishing identifying characteristics to show that Applicants were in possession of the claimed invention. The specification discloses SEQ ID NO:2 and SEQ ID NO:1, which are sufficient to distinguish the nucleic acids claimed in

claims 1 and 19, respectively. The nucleic acids in claim 24 encode a protein that comprises the amino acid sequence of SEQ ID NO:2, in which up to 10 amino acids are replaced, deleted, and/or inserted, and the protein has a specific function in maintaining smooth muscle cell differentiation. A mutation of 10 amino acids out of 414 total amino acids in SEQ ID NO:2 is equivalent to a sequence variation of about 2.3%. Therefore, the sequence of the encoded protein is more than 97% identical to SEQ ID NO:2. This sequence information, in combination with the functional characteristics, is sufficient to show possession under the Revised Interim Written Description Guidelines Training Materials ("the Written Description. Training Materials").

In Example 14 (page 53-55) of the Written Description Training Materials, the claim of interest is directed to a "protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A -> B". This claim is deemed adequate in written description because the specification discloses SEQ ID NO:3 and an assay for the A -> B reaction. Similarly, the present application discloses SEQ ID NO:2, an assay for determining the claimed function (page 6, lines 2-13), and methods for introducing mutations (page 6, lines 14-27). Therefore, one of skill in the art would recognize that Applicants were in possession of the claimed invention at the time the application was filed.

The nucleic acids of claim 30 hybridizes, after washing with 0.1xSSC and 0.1% SDS at 65°C, with the nucleic acid consisting of the nucleotide sequence of SEQ ID NO:1, and encodes a polypeptide with a specific function in maintaining smooth muscle cell differentiation. This claim is also adequately described pursuant to the Written Description Training Materials. Example 9 (pages 35-37) of the Written Description Training Materials analyzes a similar claim, directed to an isolated nucleic acid that hybridizes at 6xSSC and 65°C to a particularly disclosed sequence and encodes a protein having a specified activity. The Written Description Training Materials state that a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claim, because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. The Written Description Training Materials thus conclude that a representative number of species is disclosed, since

highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.

In the instant case, the claimed nucleic acid hybridizes to SEQ ID NO:1 after being washed at 65°C in 0.1xSSC and 0.1%SDS. The proteins encoded by the claimed nucleic acid also have a specified activity. Accordingly, the claimed invention is adequately described.

Claim 2

Claim 2 is directed to an isolated nucleic acid encoding the amino acid sequence of SEQ ID NO:2 or a fragment thereof, wherein the fragment has the specified function in maintaining smooth muscle cell differentiation. A fragment of SEQ ID NO:2, by definition, must be 100% identical to a portion of SEQ ID NO:2. This portion has to be a substantial portion, because the fragment has a function that is equivalent to that of SEQ ID NO:2. Thus, the claimed genus of functional fragments is not highly variable because the species must possess both a high degree of structural identity to SEQ ID NO:2 and a function equivalent to that of SEQ ID NO:2. Accordingly, a representative number of species is disclosed to demonstrate possession of the claimed genus, and the claimed invention is adequately described.

Claims 3-8 and 11-12 are directed to vectors comprising the nucleic acids discussed above, transformants harboring the nucleic acids or vectors, and methods of preparing polypeptides using the transformants. Since Applicants had possession of the nucleic acids, possession of the claimed subject matter of the dependent claims is evident.

Accordingly, withdrawal of this rejection is respectfully requested.

Other newly added claims

Applicants submit that all newly added claims are adequately described. Claims 19, 24 and 30 have been discussed.

Claim 18 is directed to an isolated nucleic acid encoding the polypeptide consisting of SEQ ID NO:2. Applicants have reduced this invention to practice.

Claim 35 is directed to an isolated nucleic acid encoding a polypeptide that comprises an amino acid sequence at least 95% identical to SEQ ID NO:2, wherein the polypeptide has a function associated with the maintenance of differentiation of smooth muscle cells that is equivalent to that of the protein consisting of SEQ ID NO:2. Claim 35 depends from claim 35, reciting that the amino acid sequence is at least 98% identical to SEQ ID NO:2. For the same reasons discussed above, the written description requirement is satisfied for these claims (see, for instance, Example 9 of the Written Description Training Materials).

Claims 41, 46, 52, and 57-58 are directed to nucleic acids that are structurally similar to SEQ ID NO:1 or encode polypeptides that are structurally similar to SEQ ID NO:2. Furthermore, the nucleic acids all encode an oxidoreductase. The Written Description Training Materials specifically indicate that enzyme activities are distinguishing characteristics (see, for instance, Example 8 of the Written Description Training Materials). Therefore, these claims recite both structural and functional characteristics that are sufficient to shown possession under the Written Description Guidelines.

The remaining new claims are directed to vectors comprising the nucleic acids discussed above, transformants harboring the nucleic acids or vectors, and methods of preparing polypeptides using the transformants. Since Applicants had possession of the nucleic acids, possession of the claimed subject matter of the dependent claims is evident.

Rejection Under 35 U.S.C. §112, First Paragraph, Enablement (Paragraph 7 of the Office Action)

The rejection of claims 1-8 and 11-12 under 35 U.S.C. §112, first paragraph, as allegedly not enabled, is respectfully traversed. Specifically, the Office Action alleges that the claimed invention is not supported by a patentable utility, and therefore one skilled in the art would not know how to use the claimed invention. As discussed above, the claimed invention possesses

both well-established and asserted utilities that are specific, substantial, and credible. Therefore, withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §112, Second Paragraph (Paragraph 8 of the Office Action)

The rejection of claims 1, 3, 5, 7 and 11 under 35 U.S.C. §112, first paragraph, as allegedly being indefinite, for reciting the term "stringent", is now moot since this term is no longer recited in any of the claims. Therefore, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §102 (Paragraphs 9-11 of the Office Action)

A. The rejection of claims 1-2 under 35 U.S.C. §102 in view of Gmerek *et al.* (Genbank Accession U13395) is respectfully traversed for the reasons set forth below.

The standard of anticipation under 35 U.S.C. §102 is that each and every element of the claim must be found in the cited reference. *In re Marshall*, 198 USPQ 344 (CCPA 1978).

According to the Office Action, Gmerek *et al.* teach the HHCMA56 cDNA that is 98.6% identical to positions 578 to 2052 of SEQ ID NO:1, which allegedly would hybridize to SEQ ID NO:1 and encode fragments of SEQ ID NO:2. Applicants discovered, however, that the HHCMA56 cDNA contains two nucleotide additions in the reading frame and therefore encodes an amino acid sequence that is entirely different from SEQ ID NO:2. As discussed at page 40, lines 19-25, two codons at nucleotides 276-278 and 280-282 of HHCMA56, respectively, contain only two nucleotides in SEQ ID NO:1. As a result, HHCMA56 is translated out of frame, from nucleotide 275 on, to an entirely different protein which shares only 92 residues of the 414 residues of SEQ ID NO:2. The Office Action has not established that the protein encoded by HHCAM56 meets the functional limitation of any currently pending claim in the present application.

Since Gmerek *et al.* do not teach each and every element of the claimed invention, withdrawal of this rejection is respectfully requested.

B. The rejection of claims 1-2 under 35 U.S.C. §102 as allegedly being anticipated by Applicants' own admission on page 3 is respectfully traversed for the reasons set forth below.

The Office Action states that the specification discloses on page 3:

> The results of homology search showed that the query clone was identical to the helix clone "C-T2RP3001495" [sic]. In addition, it was also revealed that the query clone is identical to the gene for Hs.519 Human oxidoreductase (HHCMAS6) [sic] of Unigene.

The Office Action thus takes the position that the claimed invention is allegedly anticipated by helix clone "C-T2RP3001495" [sic] and the gene for Hs.519 Human oxidoreductase (HHCMAS6) [sic].

Applicants wish to point out that the "HHCMAS6" in the Office Action should really be "HHCMA56" (emphasis added). See page 3 of the specification for the original text. HHCMA56 is the sequence disclosed in Gmerek *et al.* As discuss above, this sequence does not encode the protein described in the present application. Applicants also wish to bring the Examiner's attention to the disclosure immediately after the alleged "admission" on page 3:

> However, the sequence of HHCMA56 contains reading mistakes of nucleotides, and thus it has been deposited as a gene encoding a protein consisting of 371 amino acids which is entirely different from the protein of"C-NT2RP3001495". Thus, it can be stated that "C-NT2RP3001495" is a novel protein found for the first time by the present inventors.

As to "C-T2RP3001495", there is a typographical error on page 3, wherein "C-NT2RP3001495" is mistakenly written as "C-T2RP3001495". "C-NT2RP3001495" is SEQ ID NO:1 itself, and hence it does not anticipate the claimed invention. The Examiner may have been misled regarding the helix clone by the disclosure at page 40, lines 12-13 and 17-18:

> Then, cDNA sequences of the Helix Research Institute (helix clones; Japanese Patent Application No. Hei 11-248036; Japanese Patent Application No. 2000-118776) were searched ....
>
> The homology search using the helix clones revealed that the sequence was identical to that of a helix clone "C-NT2RP3001495".

Japanese Patent Application No. Hei 11-248036 and Japanese Patent Application No. 2000-118776 are priority applications of the present application, and "C-NT2RP3001495" is

the claimed invention itself. "C-NT2RP3001495" was not disclosed before the priority date. Therefore, "C-NT2RP3001495" is not prior art to the present application.

Accordingly, withdrawal of this rejection is respectfully requested.

Conclusions

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims under examination in this application is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (617) 542-5070 or the undersigned's associate, Ping Hwung, at (650) 839-5044.

Enclosed is a $1,186.00 check for excess claim fees and a $950.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 5/5/04

Reg No. 44,164

for Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906